

The role of liver transplantation in the treatment of hilar cholangiocarcinoma

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Abstract

Surgical resection or liver transplantation (LTx) are the only available treatments that offer a potential for long-term survival or cure in cases of hilar cholangiocarcinoma. Hilar resection in combination with partial hepatectomy and caudate lobectomy is regarded as the current treatment of choice. Overall 5-year survival rates range from 9% to 28%, and reach as high as 24–43% in R0 resections. Five-year survival rates in the very limited experience with LTx in hilar cholangiocarcinoma are not dramatically worse than those after resection. However, hilar cholangiocarcinoma is not at present an accepted indication for LTx given both the good results of LTx for benign diseases and the dramatic organ shortage. When compared with the prognosis of other gastrointestinal tumours, these survival rates are encouraging in the setting of an otherwise unresectable malignancy. As such, and considering the fact that it may represent the only possibility for cure, the general exclusion of patients with cholangiocarcinomas as candidates for LTx does not seem to be justified. Furthermore, recent advances in multimodal tumour therapy seem to be most promising in combination with LTx. Prospective studies are required to elucidate the influence of better patient selection and the role of multimodal treatments on the outcome of LTx in hilar cholangiocarcinoma. If the encouraging data achieved with neoadjuvant therapy prior to LTx are confirmed by further studies, we foresee that renewed interest in LTx for hilar cholangiocarcinoma could arise.

Key Words: *Hilar cholangiocarcinoma, liver transplantation, liver resection*

Introduction

Surgical resection is regarded as the current treatment of choice for hilar cholangiocarcinoma. Overall 5-year survival rates range from 9% to 28%, and reach as high as 24–43% in R0 resections [1–11]. Although recent results of the very limited experience with liver transplantation (LTx) in hilar cholangiocarcinoma are not dramatically worse than those after resection, hilar cholangiocarcinoma is currently not an accepted indication for LTx because of the satisfactory outcome of LTx for benign diseases and the dramatic organ shortage (Table I) [1,12–25].

In the early periods of LTx, irresectable hepatobiliary malignancies including hilar cholangiocarcinoma were favoured indications, as such patients were usually in good physical condition and operative technical problems were diminished by the absence of severe portal hypertension and end-stage liver disease. However, the initial good clinical outcome was followed by a high tumour recurrence rate, and most patients died within 1 or 2 years after transplantation [20,26–28]. These results led many centres to abandon LTx for cholangiocarcinoma, mostly to avoid the waste of

otherwise needed donor organs for benign diseases. As such, only few data were generated on the outcome of LTx for hilar cholangiocarcinoma, and the very few series available were hampered by small numbers of patients, lack of clear differentiation between hilar and intrahepatic cholangiocellular carcinoma, and poor stratification of results with regard to surgical radicality and tumour staging.

Our report provides an overview of the experience with LTx for hilar cholangiocarcinoma, and attempts to outline whether there is still a place for liver grafting in the management of this pathology.

LTx plus Whipple

The initial experience with LTx for hilar cholangiocarcinoma was impaired by low survival rates due to frequent tumour relapse, usually loco-regional rather than distant. In particular, a considerable incidence of tumour recurrence was observed in the region of the head of the pancreas, pointing to an inadequate resection margin at the common bile duct and upper part of the pancreas as a potential contributing factor.

Table I. Review of literature regarding liver transplantation (LTx) in hilar cholangiocarcinoma

Ref. no.	Author	Year	LTx (n)	Operative extension (n)	Neo-/adjuvant treatment (n)	Survival
12	Alessiani*	1995	12	(12) Cluster-Tx	–	25% 4 years
13	Cherqui	1995	2	(2) Whipple	(2) RTx	23 months (med.)
14	Anthuber	1996	10	(4) Whipple	–	25 months (med.)
1	Pichlmayr	1996	25	–	–	15.5 months (med.) 21.4% 3 years
15	Beckurts	1997	5	–	(5) IORT	12 months (med.)
16	Iwatsuki*	1998	38	(11) Cluster-Tx	(18) RTx ± 5-FU	12.7 cum 26% 5 years
17	Jonas	1998	14	Whipple	–	30% 4 years
18	De Vreede#	2000	11	–	(11) RTx ± 5-FU	44 months (med.)
19	Figueras**	2000	8	–	(8) RTx + 5-FU	88% 3 years
20	Shimoda	2001	5	–	–	31% 3 years
21	Sudan	2002	11	–	(11) BBT + 5-FU	17 months (med.)
22	Robles**	2004	36	–	–	55 months (cum.) 53% 3 years
23	Heimbach#	2004	28	–	RTx ± 5-FU + BBT + 5-FU/Gemcitabine	82% 5 years
24	Rea#	2005	38	–	RTx ± 5-FU + BBT + 5-FU/Gemcitabine	87% 5 years
25	Zheng	2005	5	–	–	30 months (med.) 80% 3 years

RTx, radiation therapy; IORT, intraoperative radiation therapy; BBT, biliary brachytherapy; 5-FU, 5-fluorouracil. *, ** and #: data may overlap.

In an attempt to overcome this problem, Jonas and Neuhaus proposed to extend the bile duct resection by combining LTx with partial pancreatoduodenectomy [17]. This approach eradicated the entire biliary tree and complied with the basic rule of oncologic surgery of achieving wide safety margins while carrying no dissection in tumour-bearing areas. A similar resection approach was also described by Anthuber *et al.* [14] and by Cherqui *et al.* [13]. The overall 60-day-mortality in these series was 15% (3/20). However, although with this approach the rates of potentially curative resections rose up to 93%, long-term outcome showed no significant improvement. The 4-year survival rate in 14 patients described by Neuhaus was 30%, and tumour recurrence still accounted for most deaths [3,13,14,17].

Cluster-LTx

The Starzl group introduced an even more aggressive approach by combining LTx with resection of all visceral organs derived from the foregut (liver, stomach, spleen, pancreatoduodenal complex) and part of the colon. In an analysis of 12 patients undergoing this so-called upper abdominal exenteration with subsequent cluster-transplantation (liver, pancreas, duodenum and variable amounts of jejunum) or solely liver transplantation, Alessiani *et al.* observed long-term survivals (52, 54 and 59 months) in three patients, all of them with nodal negative hilar cholangiocarcinomas. However, this procedure carried a significant morbidity, and a 3-month mortality of 17% [12]. Since postoperative deaths were associated with complications of the pancreatic graft, transplantation of the liver alone was advocated despite the onset of surgically induced diabetes. Subsequent modifications to this approach, such as the pylorus-preserving cluster operation

introduced by Launois and Jamieson, were aimed at improving nutritional results, but long-term results and large-series data are not yet available [29].

Although there is no doubt that some of the drawbacks and technical failures of LTx in combination with Whipple operations or multivisceral resections might have been overcome with increasing experience, such aggressive procedures never gained wide acceptance. The unconvincing long-term results suggest that there is a limit to the contribution made by radical resections alone.

Consequently, the importance of better patient selection and the enrolment of LTx as part of a multimodal treatment concept has gained wider acceptance. This can be explained on the one hand by the experience with LTx for hepatocellular carcinoma (HCC) in the setting of cirrhosis, where patients who could have undergone hepatic resection had better outcomes after LTx. On the other hand, significant contributions have been made by ongoing developments in oncologic surgery, where tumour resection is combined with neoadjuvant treatments.

Prognostic factors

In recent years, some more detailed analyses have been published, allowing for a better assessment of the role of LTx in the treatment of hilar cholangiocarcinoma. Although the number of transplants continues to be small, most studies show a negative prognostic correlation between survival and both lymph node involvement and tumour depth. In particular, tumours confined to the ductal wall (T1) or infiltrating the perifibromuscular connective tissue but with no involvement of vascular or adjacent structures (T2) are associated with a significantly better survival than more advanced tumours. Pichlmayr *et al.* [1] achieved

1-, 3- and 5-year survival rates of 89%, 56% and 44%, respectively, after LTx ($n=9$) for hilar cholangiocarcinoma classified as pT1N0 or pT2N0. These rates compare with 37%, 0% and 0%, respectively, for more advanced tumours. Similarly, Iwatsuki *et al.* [16] reported 1-, 3- and 5-year survival rates of 68%, 50% and 50%, respectively, in 28 transplants with negative surgical margins and negative lymph nodes. Comparable results were reported by Robles *et al.* [22] with a 5-year survival rate of 36% in 36 patients after LTx for hilar cholangiocarcinoma.

From an oncologic point of view, 5-year survival rates of 30–50% in highly selected patients with otherwise unresectable tumours are extremely good. Although these data are too few to draw further conclusions and need to be confirmed by larger series, these encouraging results suggest that a systematic denial of LTx for hilar cholangiocarcinoma does not seem to be justified. Furthermore, since these survival rates after LTx are observed in cases of otherwise unresectable tumours, one may speculate that these results may improve even further if smaller and still resectable tumours were considered. If so, there would be no reason to exclude these patients from LTx. In principle, these patients would also be candidates for cadaveric LTx, something that by current standards is not considered appropriate given the good results of LTx for benign disease. However, in a manner similar to the recent experience with LTx in HCC, marginal donors not routinely accepted for transplantation of other types of liver disease could be used for patients with hilar cholangiocarcinomas.

The reports by Iwatsuki, Pichlmayr and Robles *et al.* [1,16,22] are significant not only because they underline the importance of patient selection, but also because they illustrate the lack of diagnostic accuracy in tumour staging of hilar cholangiocarcinomas. While the T-category of hilar cholangiocarcinoma is difficult to assess preoperatively—something that limits its use as a selection criterion—the negative prognostic impact of tumour-positive lymph nodes could be addressed prior to transplantation in two possible ways. Candidates could undergo either an explorative laparotomy with complete lymphadenectomy of the hepatic hilum prior to LTx, or a systematic and complete lymphadenectomy with immediate assessment by frozen section at the time of LTx. Although the first approach carries the disadvantage of an additional surgery prior to LTx, it allows for a more accurate staging, prevents logistic problems associated with the performance of multiple frozen sections at the time of transplantation, and is not associated with a potentially longer allograft preservation time. The second approach has the disadvantage that in cases of tumour-positive lymph nodes, the switch to a back-up patient could result in further prolongation of the cold ischaemic time of the liver. Nevertheless, since patients with negative findings at staging laparotomy may still develop peritoneal carcinomatosis and intrahepatic

tumour spread while on the waiting list, back-up patients are mandatory for both approaches.

Multimodal treatment concepts

In 1998, Iwatsuki *et al.* reported on a larger number of patients ($n=22$) undergoing LTx in combination with various protocols of adjuvant external radiation therapy with or without 5-fluorouracil (5-FU) sensitization prior to and after the operation. Their results showed a significant survival benefit for patients receiving adjuvant therapy (mean survival of 16.7 months) when compared with those undergoing LTx alone (mean survival of 12.3 months). However, the difference became insignificant when patients who died within 3 months after operation were excluded from the analysis [16].

In recent years, surgical treatment of hilar cholangiocarcinoma has been further enriched by the introduction of intraoperative radiotherapy (IORT) [30]. This approach aims to address one of the main problems in resection surgery of Klatskin tumours: the development of loco-regional recurrence caused by both perineural tumour invasion and very small safety margins at the hepatic ducts. Not long ago, Sotiropoulos from our group reported on a 10-year survivor pretreated with IORT at staging laparotomy 6 weeks prior to LTx for an unresectable hilar cholangiocarcinoma [31]. Although the exact contribution of IORT to long-term survival in this single case remains undetermined, the potential of IORT in local tumour control prior to or at the time of LTx seems worthy of consideration.

Recently, very promising data from the Mayo Clinic have been reported by Heimbach *et al.* [23]. In this ongoing study, a total of 56 patients underwent neoadjuvant therapy including external beam irradiation with a radiosensitizing bolus of 5-FU chemotherapy, followed by a transcatheter Iridium-192 brachytherapy boost and either intravenous 5-FU or oral capecitabine prior to LTx. Four patients died during the therapy, and another four had evidence of tumour progression prior to completion of the neoadjuvant treatment. Fourteen of the remaining 48 patients were further excluded due to the presence of tumour-positive lymph nodes at the time of routine staging laparotomy. Twenty-eight patients underwent LTx with an operative mortality rate of 11% and a 5-year survival rate of 82%. In a subsequent follow-up expanded report of the same group by Rea *et al.* in 2005 [24], a total of 38 patients had already undergone LTx after neoadjuvant therapy, with actual 1-, 3- and 5-year survival rates of 91%, 87% and 87%, respectively.

In an approach similar to that of the Mayo Clinic, Sudan *et al.* [27] introduced a neoadjuvant protocol that included 6.000 cgy biliary brachytherapy delivered through percutaneous transhepatic catheters and intravenous 5-FU (300 mg/m²/day) until

transplantation. The drop-out rate in this study was 35% (6/17). Eleven patients were transplanted at a median of 3.4 months after diagnosis, with three of them dying in the perioperative period. Only two of the remaining eight patients experienced tumour recurrence, with five being alive without evidence of disease at a median follow-up of 7.5 years (range 2.8–14.5 years).

In Rea's series, 29 of the 38 hilar cholangiocarcinomas (76%) did not originate in a normal liver but were associated with primary sclerosing cholangitis (PSC) [24]. Similarly, in Sudan's series, 6/11 patients with hilar cholangiocarcinoma also had a diagnosis of PSC. This is of relevance, as the presence of PSC might have influenced and at least partially contributed to the excellent results of these studies. It is most likely that in patients routinely screened because of known PSC, hilar cholangiocarcinoma may be diagnosed at earlier stages than in patients without concomitant disease. In addition, concomitant liver disease may also preclude major hepatectomies despite small and potentially resectable tumours. Therefore, the results of these two studies are not completely comparable with data from most other studies that do not include hilar cholangiocarcinoma in the presence of PSC.

So far, since there is no prospective randomized study with a control group—which admittedly would be difficult to justify in view of the excellent results—it is hard to decide whether the extremely good results after LTx in these studies could be attributed to the very strong selection criteria rather than to the neoadjuvant therapy. Therefore, as long as the effects of the neoadjuvant therapy are not clearly determined, its side effects should be weighed very carefully. Regardless of such obstacles, these two approaches currently provide the most promising and encouraging treatment modalities for hilar cholangiocarcinoma, and merit both careful attention and further evaluation.

LDLTx

The increasing experience with living donor LTx (LDLTx) has led to an ongoing discussion on extended indications for LTx in hepatobiliary malignancies, in particular for HCCs not satisfying the Milan or UCSF criteria [32,33]. Such an approach offers a chance for prolonged survival or even cure for patients who would otherwise not qualify for LTx. The controversy surrounding this topic is whether it is ethically justified to subject a healthy person to the risks of a living donor hepatectomy when the prognosis of the recipient is supposed to be limited. Oncologically, in contrast to transplantation with deceased donor livers, LDLTx offers the only possibility for a scheduled transplantation after prior neoadjuvant tumour therapy, thus optimizing its effects. This becomes especially relevant when considering the Mayo Clinic and Sudan series with neoadjuvant therapy. If these data are confirmed

by further studies, the indications for LTx in hilar cholangiocarcinoma as well as a general acceptance of LDLTx will become prominent topics of discussion.

Conclusion

Five-year survival rates in the very limited experience with LTx in hilar cholangiocarcinoma are not dramatically worse than those after hilar resection in combination with partial hepatectomy. However, it is currently not accepted practice to allocate the scarce donor organs to patients suffering from hilar cholangiocarcinoma given the superior results obtained in cases of LTx for benign diseases. From an oncologic point of view, a 5-year survival rate of >30% for a highly aggressive gastrointestinal tumour is a more than acceptable result. As such, and considering the fact that it may represent the only possibility for cure, the general exclusion of patients with cholangiocarcinomas as candidates for LTx does not seem to be justified. With regard to the present dramatic organ shortage, the use of marginal donor livers otherwise not accepted for patients with end-stage liver disease could provide a much-needed alternative [34,35].

While aggressive surgical approaches such as LTx in combination with Whipple operations or upper abdominal exenterations have failed to improve the results of LTx in cases of hilar cholangiocarcinoma, recent advances in multimodal tumour therapy seem to be most promising in combination with LTx. This is particularly true in selected patients (i.e. those with lymph node-negative T1 or T2 tumours) or when concomitant liver cirrhosis precludes a partial hepatectomy in otherwise resectable cholangiocarcinomas. Since most current series of LTx for hilar cholangiocarcinoma include only cases of unresectable tumours, it would not be unreasonable to speculate that survival rates would improve even more if, in a manner similar to the experience with LTx in HCC, small and still resectable tumours were considered. Prospective studies are required to elucidate the influence of better patient selection and the role of multimodal treatment on the outcome of LTx in hilar cholangiocarcinoma. If the encouraging data achieved with neoadjuvant therapy prior to LTx are confirmed, then not only the general reluctance to proceed with LTx in cases of hilar cholangiocarcinoma will be questioned, but also a discussion about the application of LDLTx could arise.

In conclusion, reviewing the cumulated experience with LTx for hilar cholangiocarcinoma it seems worthwhile to revisit its place of indication anew.

References

- [1] Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, et al. Surgical treatment in proximal

- bile duct cancer: a single-center experience. *Ann Surg* 1996; 224:628–8.
- [2] Gerhards MF, van Gulik TM, Bosma A, ten Hoopen-Neumann H, Verbeek PC, Gonzalez DG, et al. Long-term survival after liver resection of proximal bile duct carcinoma (Klatskin tumors). *World J Surg* 1999;23:91–6.
 - [3] Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999;230:808–18; discussion 819.
 - [4] Hemming AW, Reed AI, Fujita S, Foley DP, Howard RJ. Surgical management of hilar cholangiocarcinoma. *Ann Surg* 2005;241:693–702.
 - [5] Otto G, Thies J, Hoppe-Lotichius M, Bittinger F, Pitton MB, Hadian A. Hiläres Cholangiokarzinom – Ergebnisse bei En-bloc-Resektion von Tumor und Leber. *Chirurg* 2004; 75:59–65.
 - [6] Miyazaki M, Ito H, Nakagawa K, Ambiru S, Shimizu H, Okaya T, et al. Parenchyma-preserving hepatectomy in the surgical treatment of hilar cholangiocarcinoma. *J Am Coll Surg* 1999; 189:575–83.
 - [7] Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BSJ, et al. Staging, resectability and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; 234:507–17.
 - [8] Tsao JL, Nimura Y, Kamiya J, Hajakawa N, Kondo S, Nagino M, et al. Management of hilar cholangiocarcinoma – comparison of an American and a Japanese experience. *Ann Surg* 2000;232:166–74.
 - [9] Todoroki T, Kawamoto T, Koike N, Takahashi H, Yoshida S, Kashiwagi H, et al. Radical resection of hilar bile duct carcinoma and predictors of survival. *Br J Surg* 2000; 87:306–13.
 - [10] D’Angelica M, Jarnagin WR, Blumgart LH. Surgical therapy and survival prospects in hilar cholangiocarcinoma. *HPB* 2003;5:6–10.
 - [11] Klempnauer J, Ridder GJ, Werner M, Weimann A, Pichlmayr R. What constitutes long term survival after surgery for hilar cholangiocarcinoma? *Cancer* 1997;79:26–34.
 - [12] Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of five-year experience with abdominal organ cluster transplantation. *J Am Coll Surg* 1995;180:1–9.
 - [13] Cherqui D, Alon R, Piedbois P, Duvoux C, Dhumeaux D, Julien M, et al. Combined liver transplantation and pancreatoduodenectomy for irresectable hilar bile duct carcinoma. *Br J Surg* 1995;82:397–8.
 - [14] Anthuber M, Schauer R, Jauch KW, Krämling HJ, Schildberg FW. Erfahrungen mit der Lebertransplantation und der Lebertransplantation in Kombination mit Whipple’scher Operation beim Klatskin-Tumor. *Langenbeck’s Arch Chir* 1996;Suppl II:413–15.
 - [15] Beckurts KTE, Hölscher AH, Bauer TH, Siewert JR. Maligne Tumoren der Hepaticusgabel – Ergebnisse der chirurgischen Therapie und Prognosefaktoren. *Chirurg* 1997;68:378–84.
 - [16] Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg* 1998;187:358–364.
 - [17] Jonas S, Kling N, Guckelberger O, Keck H, Bechstein WO, Neuhaus P. Orthotopic liver transplantation after extended bile duct resection as treatment of hilar cholangiocarcinoma. First long-term results. *Transpl Int* 1998;11:206–8.
 - [18] De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoradiation for cholangiocarcinoma. *Liver Transplant* 2000;6:309–16.
 - [19] Figueras J, Llado L, Valls C, Serrano T, Ramos E, Fabregat J, et al. Changing strategies in diagnosis and management of hilar cholangiocarcinoma. *Liver Transplant* 2000;6:786–94.
 - [20] Shimoda M, Farmer DG, Colquhoun SD, Rosove M, Ghobrial RM, Yersiz H, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. *Liver Transplant* 2001;7:1023–33.
 - [21] Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B, McCashland T, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002;2:774–9.
 - [22] Robles R, Figueras J, Turrion VS, Margarit C, Moya A, Varo E, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004;239:265–71.
 - [23] Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. *Semin Liver Dis* 2004;24:201–7.
 - [24] Rea JG, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005;242:451–8; discussion 458–61.
 - [25] Zheng SS, Shi QF, Liang TB, Wu J, Wang WL, Shen Y, et al. Orthotopic liver transplantation for patients with Klatskin tumor. *Hepatobiliary Pancreat Dis Int* 2005;4:28–31.
 - [26] Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000;69:1633–7.
 - [27] Goldstein RM, Stone M, Tillery GW, Senzer N, Levy M, Husberg BS, et al. Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg*. 1993;166:768–71; discussion 771–2.
 - [28] Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992;215:31–8.
 - [29] Launois B, Jamieson GG. Pylorus-preserving ‘cluster’ operation. *Br J Surg* 1991;78:1015.
 - [30] Todoroki T. Radiotherapy as a component of multidisciplinary treatment of bile duct cancer: a surgeon’s perspective. *J Hepatobiliary Pancreat Surg* 2001;8:130–6.
 - [31] Sotiropoulos G, Lang H, Niebel W, Malagó M, Broelsch CE. 10 years tumor-free survival after intraoperative radiation therapy and secondary liver transplantation for hilar cholangiocarcinoma. *Transplantation* 2004;77:1625.
 - [32] Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transplant* 2002;8:765–74.
 - [33] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–9.
 - [34] Sotiropoulos GC, Paul A, Molmenti E, Lang H, Frilling A, Napieralski BP, et al. Liver transplantation for hepatocellular carcinoma in cirrhosis within the Eurotransplant area: an additional option with “livers that nobody wants”. *Transplantation* 2005;80:897–902.
 - [35] Busuttill RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transplant* 2003;9:651–63.